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Notice of Opposition to a European Patent

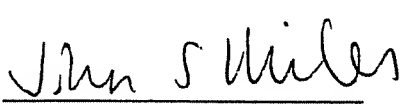
To the
European Patent Office

Tabulation Marks

		for EPO use only	
I. Patent opposed		Opp. No.	OPPO (1)
Patent No.		EP 1 141 274 B1	
Application No.		00902354.0	
Date of mention of the grant in the European Patent Bulletin (Art. 97(4), 99(1) EPC)		10 September 2003	
Title of the invention: Soluble receptor BR43X2 and methods of using them for therapy			
II. first named in the patent specification		ZymoGenetics, Inc	
Proprietor of the Patent			
Opponent's or representative's reference (max. 15 spaces)		CORW/M11157EP	OREF
III. Opponent		OPPO (2)	
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Multiple opponents	<input type="checkbox"/> further opponents see additional sheet		
IV. Authorisation		OPPO (9)	
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2. Employee(s) of the opponent authorised for these opposition proceedings under act. 133(3) EPC	Name(s):		
Authorisation(s)	<input type="checkbox"/> not considered necessary		
To 1./2.	<input type="checkbox"/> has/have been registered under No. <input type="text"/>		
	<input type="checkbox"/> is/are enclosed		

<p>V. Opposition is filed against</p> <p>— the patent as a whole <input checked="" type="checkbox"/></p> <p>— claim(s) No(s). <input type="text"/></p>	<p>for EPO use only</p>
<p>VI. Grounds for opposition:</p> <p>Opposition is based on the following grounds:</p> <p>(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:</p> <p>— it is not new (Art. 52(1); 54 EPC) <input checked="" type="checkbox"/></p> <p>— it does not involve an inventive step (Art.52(1); 56 EPC) <input checked="" type="checkbox"/></p> <p>— patentability is excluded on other grounds, i.e. <input type="text"/> Art. <input type="text"/></p> <p>(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). <input checked="" type="checkbox"/></p> <p>(c) the subject-matter of the patent opposed extends beyond the content of the application/ of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). <input checked="" type="checkbox"/></p>	
<p>VII. Facts and arguments (Rule 55(c) EPC) presented in support of the opposition are submitted herewith on a separate sheet (annex 1)</p>	<input checked="" type="checkbox"/>
<p>VIII. Other requests:</p> <p>In the event that the Opposition Division is minded to uphold the patent in full or in part, we request oral proceedings.</p>	

IX. Evidence presented		for EPO use only
Enclosed = <input checked="" type="checkbox"/>		
will be filed at a later date = <input type="checkbox"/>		
A. Publications: See list on pages 26 and 27 of opposition submission.		Publication date
1		
Particular relevance (page, column, line, fig.):		
2		
Particular relevance (page, column, line, fig.):		
3		
Particular relevance (page, column, line, fig.):		
4		
Particular relevance (page, column, line, fig.):		
5		
Particular relevance (page, column, line, fig.):		
6		
Particular relevance (page, column, line, fig.):		
7		
Particular relevance (page, column, line, fig.):		
Continued on additional sheet		<input type="checkbox"/>
B. Other evidence		
D1 Table		
D13 Alignment of human and mouse TACI		
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X. Payment of the opposition fee is made		for EPO use only																						
<input type="checkbox"/> as indicated in the enclosed voucher for payment of fees and costs (EPO Form 1010) <input checked="" type="checkbox"/> was paid by online fee payment on 2 June 2004 (copy attached)																								
XI. List of documents: <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; font-size: small;">Enclosure No.:</th> <th style="text-align: left; font-size: small;">No. of copies</th> </tr> </thead> <tbody> <tr> <td style="padding: 2px 5px;">0 <input checked="" type="checkbox"/> Form for notice of opposition</td> <td style="padding: 2px 5px;"><div style="border: 1px solid black; display: inline-block; width: 30px; text-align: center;">2</div> (min. 2)</td> </tr> <tr> <td style="padding: 2px 5px;">1 <input checked="" type="checkbox"/> facts and arguments (see VII.)</td> <td style="padding: 2px 5px;"><div style="border: 1px solid black; display: inline-block; width: 30px; text-align: center;">2</div> (min. 2)</td> </tr> <tr> <td colspan="2" style="padding: 2px 5px;">2 Copies of documents presented as evidence (see IX.)</td> </tr> <tr> <td style="padding: 2px 5px;">2a <input checked="" type="checkbox"/> — Publications</td> <td style="padding: 2px 5px;"><div style="border: 1px solid black; display: inline-block; width: 30px; text-align: center;">2</div> (min. 2 of each)</td> </tr> <tr> <td style="padding: 2px 5px;">2b <input checked="" type="checkbox"/> — Other documents</td> <td style="padding: 2px 5px;"><div style="border: 1px solid black; display: inline-block; width: 30px; text-align: center;">2</div> (min. 2 of each)</td> </tr> <tr> <td style="padding: 2px 5px;">3 <input type="checkbox"/> Signed authorisation(s) (see IV.)</td> <td style="padding: 2px 5px;"><div style="border: 1px solid black; display: inline-block; width: 30px; height: 15px;"></div></td> </tr> <tr> <td style="padding: 2px 5px;">4 <input checked="" type="checkbox"/> Voucher of payment of fees and costs (see X.)</td> <td style="padding: 2px 5px;"><div style="border: 1px solid black; display: inline-block; width: 30px; text-align: center;">1</div></td> </tr> <tr> <td style="padding: 2px 5px;">5 <input type="checkbox"/> Cheque</td> <td style="padding: 2px 5px;"><div style="border: 1px solid black; display: inline-block; width: 30px; height: 15px;"></div></td> </tr> <tr> <td style="padding: 2px 5px;">6 <input type="checkbox"/> Additional sheet(s))</td> <td style="padding: 2px 5px;"><div style="border: 1px solid black; display: inline-block; width: 30px; height: 15px;"></div> (min. 2 of each)</td> </tr> <tr> <td style="padding: 2px 5px;">7 <input type="checkbox"/> Other (please specify here):</td> <td style="padding: 2px 5px;"><div style="border: 1px solid black; display: inline-block; width: 30px; height: 15px;"></div></td> </tr> </tbody> </table>		Enclosure No.:	No. of copies	0 <input checked="" type="checkbox"/> Form for notice of opposition	<div style="border: 1px solid black; display: inline-block; width: 30px; text-align: center;">2</div> (min. 2)	1 <input checked="" type="checkbox"/> facts and arguments (see VII.)	<div style="border: 1px solid black; display: inline-block; width: 30px; text-align: center;">2</div> (min. 2)	2 Copies of documents presented as evidence (see IX.)		2a <input checked="" type="checkbox"/> — Publications	<div style="border: 1px solid black; display: inline-block; width: 30px; text-align: center;">2</div> (min. 2 of each)	2b <input checked="" type="checkbox"/> — Other documents	<div style="border: 1px solid black; display: inline-block; width: 30px; text-align: center;">2</div> (min. 2 of each)	3 <input type="checkbox"/> Signed authorisation(s) (see IV.)	<div style="border: 1px solid black; display: inline-block; width: 30px; height: 15px;"></div>	4 <input checked="" type="checkbox"/> Voucher of payment of fees and costs (see X.)	<div style="border: 1px solid black; display: inline-block; width: 30px; text-align: center;">1</div>	5 <input type="checkbox"/> Cheque	<div style="border: 1px solid black; display: inline-block; width: 30px; height: 15px;"></div>	6 <input type="checkbox"/> Additional sheet(s))	<div style="border: 1px solid black; display: inline-block; width: 30px; height: 15px;"></div> (min. 2 of each)	7 <input type="checkbox"/> Other (please specify here):	<div style="border: 1px solid black; display: inline-block; width: 30px; height: 15px;"></div>	
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XII. Signature of opponent or representative <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> Place Nottingham, England Date 3 June 2004 </div> <div style="width: 60%; text-align: center;">  <div style="border-top: 1px solid black; width: 100%; margin: 2px 0;"></div> John S Miles </div> </div> <p style="font-size: x-small; margin-top: 10px;">Please print name under signature. In the case of legal persons, the position which the person signing holds within the company should also be printed.</p>																								

European Patent No 1 141 274 B1
(European Patent Application No 00902354.0)

Zymogenetics, Inc

Opposition by Corixa Corporation

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REQUESTS

1. We request revocation of the Patent in its entirety in all contracting states on the grounds that the Patent does not satisfy Article 123(2) EPC (100(c) EPC), Article 83 EPC (Article 100(b) EPC), Article 54 EPC and Article 56 EPC (Article 100(a) EPC). In addition, the claims are directed at subject matter that cannot be considered to be an invention eligible for patent protection contrary to Article 52(1) EPC (Article 100(a) EPC).
2. If the Opposition Division (OD) believes that any reference to BCMA is required to remain in the Patent, we also request correction of page 3, line 53 of the Patent to indicate that TACI is represented by SEQ ID No: 6 and that BCMA is represented by SEQ ID No 8.
3. A replacement page 6 of the application was filed with the Patentee's letter dated 6 August 2001 upon entering the European regional phase. That letter states:

"Please note that there is a typographical error on page 6, line 34, where the BCMA amino acid sequence is designated as "SEQ ID No: 6". The correct reference is SEQ ID No: 8, which can be found on page 15 (line 5), page 57 (lines 34 to 35), and Figure 1. In addition, there is an erroneous reference to "SEQ ID No: 7" as the BR43x1 amino acid sequence on page 6, line 35. The correct reference is SEQ ID No: 9, which can be verified by comparing that sequence with the BR43x1 amino acid sequence shown in Figure 1".

4. We agree with this analysis. Unfortunately, however, replacement page 6 filed with the 6 August 2001 letter has been amended to indicate erroneously that TACI is SEQ ID No: 8 and that BCMA is SEQ ID No: 6, whereas the correction should have indicated that TACI is SEQ ID No: 6 and BCMA is SEQ ID No: 8.
5. We request oral proceedings in the event that the OD is not able to grant the above requests based on our written submissions.

THE PATENT UNALLOWABLY ADDS SUBJECT MATTER

Claim 3

6. Claim 3 refers to the given compounds being used in the manufacture of a medicament "*for inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement*". This claim wording was introduced with the Patentee's letter dated 2 October 2002 and the Patentee suggests that a basis is provided at page 2, lines 7 to 12; page 54, lines 18 to 20; and page 75, lines 33 to 36. In each case, the Patentee suggests that ztnf4 is a preferred ligand.
7. The previous wording, which is found, for example, in Claim 29 as filed, is "*for inhibiting BR43x2, TACI or BCMA receptor-ligand engagement*".
8. Nowhere in the application as filed is there any disclosure of inhibiting *only* the receptor-ztnf4 engagement and not also other receptor-ligand engagements. Indeed, there is nothing in the application as filed which teaches that the listed compounds inhibit receptor-ztnf4 engagement but without also inhibiting receptor-ligand engagements *generally*. As discussed in detail below this also gives rise to a lack of sufficiency of disclosure.
9. Page 2, lines 7 to 12 of the application as filed (referred to by the Patentee as giving a basis for the claim) relates only to modulating the activity of ztnf4 or other BR43x2, TACI or BCMA ligands and does not discuss receptor engagement. Page 54, lines 18 to 20 refers to bioassays and ELISAs to measure cellular response to ztnf4 and does not disclose inhibition of receptor engagement. Page 75, lines 33 to 36 refers only to diagnostic systems. Thus, none of these relate to the specific concept of inhibiting receptor-ztnf4 engagement (which is the subject matter of the amended claim).
10. Clearly, if Claim 3 was amended back to use the original term "receptor-ligand engagement" there would be an unallowable increase in the scope of protection since the medicament would be for inhibiting other receptor-ligand engagements, not just receptor-ztnf4 engagement, in which case Article 123(3) EPC would be contravened.
11. As discussed in detail below in relation to lack of novelty under Article 54(3) EPC, at least BCMA binds more than one ligand (ie ztnf4 (also called BAFF) and APRIL).

Claims 13 to 28

12. Claims 13 to 28 appear to be based, at least superficially, on Claims 10 to 28 of the application as filed, all of which claims are ultimately dependent on Claim 1.
13. Each of Claims 10 to 28 as filed state that "*ztnf4 activity is associated with*" eg B lymphocytes (Claim 10), antibody production (Claim 13), asthma (Claim 16) and so on.
14. In contrast, each of the claims of the Patent indicate that the "*medicament is for*" treatment of B lymphocytes (Claim 13), inhibiting antibody production (Claim 16), treatment of asthma (Claim 19) and so on.
15. Thus, these claims are directed at subject matter (ie direct uses of the medicament) which is not taught in the application as filed (where only inhibition of ztnf4 activity is taught and that this activity may be associated with different cell types or medical conditions).
16. If the OD does not accept that there is unallowable addition of subject matter, they must at the very least accept that a disclosure in the prior art of treating any of the specific diseases listed in these claims with anti-TACI or anti-BCMA antibodies is a disclosure of using such antibodies to "inhibit ztnf4 activity" or to "inhibit TACI or BCMA-ztnf4 engagement" since there is no technical teaching in the Patent of what is required to "inhibit ztnf4 activity" or "inhibit TACI or BCMA-receptor engagement" when treating these diseases which is not either given in, or obvious from, the prior art which teaches or suggests using anti-TACI or anti-BCMA antibodies to treat the same diseases.

Claims 36 to 38

17. Claims 36 to 38 relate to pharmaceutical compositions *generally* which contain the given antibody or antibody fragments.
18. These claims were introduced by the Patentee (as Claims 34 to 36) upon entering the European regional phase. They are not present in the claims of the application as filed, and no basis was given for them.

19. There is no basis. The only *general* disclosure of pharmaceutical compositions is given on page 83, line 24 to page 84, line 15 and this relates to BR43x2, TACI or BCMA polypeptides and *not* to antibodies or fragments thereof.

LACK OF NOVELTY UNDER ARTICLE 54(3) EPC

Much of the claimed subject matter is not entitled to priority

20. The Patent claims the priority of US Patent Application No 09/226,533 dated 7 January 1999 (Zymo I). Much of the claimed subject matter is not present in Zymo I as set out in more detail below and so is not entitled to priority.
21. In order to assist the OD, we refer to D1 which is a Table that shows the different names used for the same molecules and the different SEQ ID Nos used for the same molecules in the Patent and in Zymo I.

There is no disclosure of antibodies which specifically bind BCMA (SEQ ID No 8 of the Patent) in Zymo I

22. As can be seen from the Table (D1), SEQ ID No 8 of the Patent is BCMA which, in Zymo I, is represented by SEQ ID No 6 (see, for example, page 2, line 13 of Zymo I).
23. There is no disclosure anywhere in Zymo I of an antibody which specifically binds BCMA (SEQ ID No 8 of the Patent; SEQ ID No 6 of Zymo I). For example, antibodies are discussed at page 4, lines 24 to 28 of Zymo I (embodiments (f) and (g)) but these antibodies are ones which are directed at SEQ ID No 4 and SEQ ID No 8 (SEQ ID No 4 and SEQ ID No 10 of the Patent). A similar disclosure is also found on page 53, lines 3 to 23 and in Claim 3. Page 57, line 18 to page 64, line 26 relates to antibodies but, again, there is no disclosure of anti-BCMA antibodies.
24. Thus, to the extent that the claims encompass an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID No 8 (BCMA; SEQ ID No 6 in Zymo I) none of Claims 1 to 28 and 36 to 38 are entitled to priority.

There is no disclosure of antibodies which specifically bind TACI (SEQ ID No 6 of the Patent) in Zymo I

25. SEQ ID No 6 (TACI) of the Patent is not present in Zymo I. SEQ ID No 5 of Zymo I appears to be a truncated version of TACI (compare SEQ ID No 5 of Zymo I which is 199 amino acid residues and SEQ ID No 6 of the Patent which is 293 amino acid residues).
26. In any event, there is no disclosure of antibodies which specifically bind SEQ ID No 5 (truncated TACI) in Zymo I. Thus, to the extent that the claims encompass an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID No 6 (TACI), none of Claims 1 to 28 and 36 to 38 are entitled to priority.

There is no disclosure of antibodies which bind the SEQ ID No 20 polypeptide in Zymo I

27. The polypeptide of SEQ ID No 20 of the Patent and antibodies which bind specifically thereto are not disclosed in Zymo I. Therefore, Claim 3 and claims dependent thereon are not entitled to priority (at least to the extent that they refer to SEQ ID No 20). The polypeptide of SEQ ID No 20 appears to be murine TACI.

WO 01/12812 (D2) is prior art under Article 54(3) EPC

28. D2 validly entered the European regional phase as European Patent Application No 00957502.8 (EP 1 210 425 A) in March 2002 and designates all contracting states in common with the Patent. Therefore, D2 is available as prior art under Article 54(3) and (4) EPC.
29. D2a (US Patent Application No 60/149,378) is the first priority application of D2 and is dated 17 August 1999. Therefore, the contents of D2a which are also present in D2 as published are available to attack the novelty of the claims of the Patent not entitled to priority.

WO 01/24811 (D3) is prior art under Article 54(3) EPC

30. D3 validly entered the European regional phase as European Patent Application No 00968780.7 (EP 1 223 964 A) in May 2002 and designates all contracting states in common with the Patent. Therefore, D3 is available as prior art under Article 54(3) and (4) EPC.
31. D3a (US Patent Application No 60/157,933) is the first priority application of D3 and is dated 6 October 1999. Therefore, the contents of D3a which are also present in D3 as published are available to attack the novelty of the claims of the Patent not entitled to priority.

Claim 1 lacks novelty over D2 and D3

32. As discussed above, at least features (g) and (h) of Claim 1 are not entitled to priority (ie antibodies or antibody fragments which specifically bind to a polypeptide of SEQ ID No 6 (TACI) or SEQ ID No 8 (BCMA)).
33. Claim 1 lacks novelty over D2 for the following reasons. In relation to feature (h), Claim 1 is directed at an antibody to BCMA being used in the manufacture of a medicament for inhibiting ztnf4 activity in a mammal. It is plain that ztnf4 activity is inhibited by the antibody binding to BCMA which is a receptor for ztnf4.
34. D2 describes the interaction between BCMA (called BAFF-R in D2; see page 1, lines 22 of D2; see page 2, line 19 of the Patent; and compare SEQ ID No 8 of the Patent with SEQ ID No 1 of D2 and D2a shown in Figure 1) and BAFF (which is the same as ztnf4; see Patent at page 2, line 19). See also Table 1 (D1).
35. D2a describe antibodies which specifically bind to BCMA (BAFF-R) (see, for example, page 5, lines 15 and 16 and these antibodies are used in a medicament for inhibiting ztnf4 (BAFF) activity in a mammal. This is clear from, for example, Claims 21, 27, 33, 39, 45, 62 to 65, 67, 69, 81 and 82 of D2a all of which refer to the use of antibodies specific for BCMA (BAFF-R) for treating a range of diseases and conditions. (Equivalent disclosures are found in Claims 1 to 7 and 16 to 18). Claims 25, 31, 37, 43, 51 and 60 of D2a (and Claim 14 of D2) make it clear that mammals are treated.

36. Claims 62, 63 and 67 of D2a (Claim 16 of D2) are particularly noteworthy since they specifically indicate that an agent is used which is capable of interfering with the association between BAFF-R and BAFF (ie BCMA and ztnf4). Page 22, lines 9 to 11 of D2a make it clear that antibodies are such agents (see also page 21, lines 21 to 23 of D2).
37. Thus, Claim 1 lacks novelty over D2.
38. Claim 1 lacks novelty over D3 for the following reasons. As noted above, feature (h) of Claim 1 is directed at an anti-BCMA antibody.
39. D3 describes the interaction between BCMA (called APRIL-R in D3; see page 4, lines 10 to 13 of D3; and page 4, lines 20 and 21 of D3a).
40. D3a at page 4, lines 29 to 30 indicates that anti-APRIL-R antibodies (ie anti-BCMA antibodies) may be used in the treatment of cancer, and Claims 16 to 19 of D3a discloses the use of anti-BCMA antibodies in treating a mammal for a condition associated with undesired cell proliferation. (Equivalent disclosures are found in D3 at, for example, page 4, lines 17 to 21 and in Claim 1).
41. While there may be no explicit disclosure in D3 that the anti-APRIL-R (ie anti-BCMA) antibodies inhibit ztnf4 activity, we submit that this is an inherent property of the antibodies disclosed in D3 since antibodies, which inhibit APRIL binding to APRIL-R (BCMA) will also inhibit ztnf4 binding to BCMA because APRIL and ztnf4 bind to overlapping sites on BCMA. This is demonstrated in D4 (Patel *et al* (2004) *J. Biol. Chem.* 279, 16727-16735) which, although not prior art, is evidence of an inherent property of BCMA (see, for example, Figure 3 which shows that residues D15, L17 and L18 are all involved in the binding site for BAFF and APRIL on BCMA). Because of the close proximity of these residues in BCMA (see Figure 5) an antibody which blocks the binding of one ligand by virtue of its size also blocks the binding of the other ligand through steric hindrance.
42. In any event, D3a at page 23, lines 5 to 8, indicates that antagonistic anti-BCMA receptor antibodies of the invention have the ability to inhibit receptor-ligand interactions (ie not just receptor-APRIL interactions).
43. If the Patentee should argue that there is not a sufficient disclosure in D3 of inhibiting ztnf4 activity, we note that there is no disclosure in

the Patent of how to make anti-BCMA antibodies which *only* inhibit ztnf4 activity (and do not, for example, inhibit APRIL activity also. As noted above, APRIL also binds to BCMA). In other words, there is nothing different in the teachings in the Patent or D3 of anti-BCMA antibodies or how to use them therapeutically.

44. To put it another way, the disclosure of the use of anti-BCMA antibodies to treat a patient for any condition is inevitably a disclosure of using those antibodies for inhibiting ztnf4 activity. If it is not, then the Patent must lack sufficiency since it teaches nothing more than in D3 (or D2) on how to make anti-BCMA antibodies and use them therapeutically.

Claim 2 lacks novelty over D2 and D3

45. Claim 2 stipulates that the mammal to be treated is a primate. The treatment of humans with the anti-BCMA antibodies is disclosed in D2a, for example, in Claims 26, 32, 38, 44, 52 and 61 (see, for example, Claim 15 in D2). Thus, Claim 2 lacks novelty over D2.
46. Claim 2 also lacks novelty over D3 (see Claim 6 of D3a; Claim 11 of D3).

Claim 3 lacks novelty over D2 and D3

47. Claim 3 indicates that the medicament is for inhibiting BCMA receptor-ztnf4 engagement. This is precisely what is taught in D2a in, for example, Claim 67 ("interfering with association of BAFF-R and BAFF"; see also Claim 16 of D2).
48. Thus, Claim 3 lacks novelty over D2 for effectively the reasons given in relation to Claim 1.
49. Claim 3 also lacks novelty over D3 effectively for the same reasons as Claim 1. In particular, it is noted that since APRIL and ztnf4 bind to overlapping sites on BCMA the anti-BCMA antibodies of D3 will inhibit BCMA receptor-ztnf4 engagement in the same way that they prevent BCMA-APRIL engagement in D3 (see page 23, lines 6 to 8 of D3a and page 28, lines 20 to 22 of D3).
50. As noted in relation to Claim 1, there is no teaching in the Patent of how to make antibodies which are *only* able to inhibit BCMA-ztnf4

engagement which do not also inhibit *any* BCMA-ligand engagement.

Claim 13 lacks novelty over D2 and D3

51. Claim 13 is directed at the medicament being used for “treatment of B lymphocytes”. This is disclosed in D2a, for example in Claim 21 (“a method of inhibiting B-cell growth”; see also Claim 1 of D2).
52. It is also disclosed in D3a (see Claim 1; also see page 11 of D3 where APRIL-R related molecules (eg antibodies) are suggested for use to effect the growth and maturation of B-cells).

Claim 14 lacks novelty over D2

53. Claim 14 is directed at the medicament being used for “treatment of activated B lymphocytes”. Claim 21 of D2a is implicitly a disclosure of treating activated B lymphocytes since the B cells to be treated are growing. Similarly, Claim 63 of D2a refers to treating, suppressing or altering an immune response which is implicitly a disclosure of treating activated B lymphocytes. Equivalent disclosures are also found in Claims 1 and 2 of D2.

Claim 15 lacks novelty over D2 and D3

54. The first paragraph of both D2a and D2 refers to the use of blocking agents (eg antibodies) to BCMA (BAFF) receptor to inhibit expression of B-cells and immunoglobulin. Since the B-cells are not expressing immunoglobulin, they are “resting” (ie have not been activated into mature antibody-secreting cells).
55. The disclosures in D3a and D3 referred to in relation to Claim 13 are of treatment of resting B lymphocytes (ie to *effect* the growth and maturation of B lymphocytes) which implies that the B lymphocytes are resting before treatment).

Claim 16 lacks novelty over D2

56. Claim 16 is directed at the medicament being used for inhibiting antibody production. This is disclosed in Claim 27 of D2a (see also Claim 2 of D2).

Claim 17 lacks novelty over D2

57. Claim 17 is directed at the medicament being used for treating an autoimmune disease. This is disclosed in D2a in, for example, Claim 45 (see Claim 4 of D2).

Claim 19 lacks novelty over D2

58. Claim 19 is directed at the medicament being used to treat, *inter alia*, end stage renal failure. This is disclosed in D2a in Claims 78 and 79 where renal disorders are treated with a B-cell growth inhibitor of which anti-BCMA inhibitors are examples (see Claim 21 of D2a). See also Claim 6 of D2.

Claim 21 lacks novelty over D2

59. Claim 80 of D2a is directed at "A method of treating B-cell lympho-proliferative disorders comprising the step of administering a therapeutically effective amount of a B-cell growth inhibitor" (see also Claim 7 of D2). A lympho-proliferative disorder is a lymphoma hence Claim 21 lacks novelty over D2.

Claim 27 lacks novelty over D2

60. Claim 27 is directed at the medicament being for the treatment of inflammation. This is disclosed in D2a, for example in Claims 64 and 65 (see also Claim 18 of D2).

Claim 36 lacks novelty over D2 and D3

61. As discussed above, at least features (c) and (d) of Claim 36 are not entitled to priority (ie antibodies or antibody fragments which specifically bind to a polypeptide of SEQ ID No 6 (TACI) or SEQ ID No 8 (BCMA)).
62. Claim 36 lacks novelty over D2 since pharmaceutical compositions of antibodies to BCMA are disclosed in D2a/D2 as discussed above in relation to Claim 1, where the antibodies are used in the

manufacture of a medicament (and therefore are, implicitly, made into pharmaceutical compositions).

63. If the Patentee argues that there is no disclosure of pharmaceutical compositions in D2a/D2, then there is also no such disclosure in the Patent (see comments on Claim 36 in the section on unallowable addition of subject matter).
64. Claim 36 also lacks novelty over D3. D3a at page 5, lines 1 to 3 discloses pharmaceutical compositions of selected cancer therapeutic agents of the invention. Page 4, lines 27 to 30 of D3a make it clear that anti-APRIL-R (anti-BCMA) antibodies are such agents. Equivalent disclosures are found in D3 on page 4, lines 17 to 25.

Claim 37 lacks novelty over D2 and D3

65. Claim 37 lacks novelty over D2 for the same reason as Claim 36 and because D2a discloses antisera (ie polyclonal antibodies) and monoclonal antibodies on page 12, line 15; murine antibodies on page 12, line 17; and humanised antibodies on page 13, line 23 *et seq.* Equivalent disclosures are also found in D2, page 12, line 19 to page 14, line 17).
66. Claim 37 also lacks novelty over D3 for the same reason as Claim 36 and because D3a describes the various types of antibodies (see page 13, line 16 to page 15, line 17; equivalent disclosures are found in D3, page 13, line 17 to page 15, line 15).

Claim 38 lacks novelty over D2 and D3

67. Claim 38 lacks novelty for the same reason as Claim 36 and because antibody fragments are described on page 13, lines 6 to 15 of D2a (page 13, lines 11 to 21 of D2) and on page 14, lines 9 to 19 of D3a (page 14, lines 9 to 19 of D3).

LACK OF NOVELTY UNDER ARTICLE 54(2) EPC

WO 98/39361 (D5)

68. WO 98/39361 (D5) was published on 11 September 1998 and so is fully available as prior art. It relates to the molecular investigation of TACI (ie SEQ ID No 6 of the Patent) and, in particular, to the therapeutic use of antibodies thereto.
69. We refer the OD to page 49, line 21 to page 52 line 16 which gives a full description of how to make anti-TACI antibodies including those that antagonise the activity of TACI protein (see page 52, lines 14 to 16). We also refer to page 58, lines 1 to 28 which describes therapeutic methods by antagonising TACI activity using anti-TACI antibodies.

Claim 1 lacks novelty over D5

70. That D5 destroys the novelty of Claim 1 is highlighted by consideration of, for example, Claim 27 which relates to the treatment of inflammation and is dependent on Claim 1. D5 at page 58, lines 8 to 10 describe the use of anti-TACI antibodies which antagonise TACI activity to treat inflammatory diseases. Since the treatment of inflammation is the subject of Claim 27 which is dependent on Claim 1, Claim 1 (as well as Claim 27) must lack novelty. It is completely irrelevant that there is no explicit mention of the inhibition of ztnf4 activity in D5 since the use of the anti-TACI antibody for treatment of inflammatory disease is an inherent disclosure of this.
71. It should be noted that Claim 1, part (g) allows for *any* antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID No 6 (TACI).

Claim 3 lacks novelty over D5

72. Claim 3 lacks novelty over D5 essentially for the same reason as Claim 1 since the use of anti-TACI antibodies which antagonise TACI activity in D5 to treat, for example, inflammatory disease is an inherent disclosure of them being used to inhibit receptor-ztnf4 engagement.

73. The polypeptide of SEQ ID No 20 appears to be murine TACI. Because of the similarity in amino acid sequence between human and mouse TACI (compare SEQ ID Nos 6 and 20 of the Patent) antibodies to human TACI described in D5 will also bind mouse TACI. Should the Patentee argue that the antibodies in D5 are not "specific" for mouse TACI, we would point out that there is no disclosure in the Patent on how to make antibodies for human TACI which would not also bind mouse TACI. We refer to D13 which is an alignment of human and mouse TACI amino acid sequences.
74. There is significant homology between the cysteine-rich pseudorepeats indicating that cross-reactive antibodies would be generated.

Claim 13 lacks novelty over D5

75. Since TACI is expressed in B lymphocytes and the patient to which anti-TACI antibodies which antagonise TACI activity administered in D5 contain B lymphocytes, "treatment of B lymphocytes" is described in D5 and Claim 13 lacks novelty.

Claim 14 lacks novelty over D5

76. D5 discloses slowing the proliferation of B cells which are cancerous (page 16, lines 28 to 31) which B cells plainly are activated.

Claim 15 lacks novelty over D5

77. The prevention of activation of B lymphocytes (which, therefore, are resting B lymphocytes if they have not been activated) is described on page 16, lines 24 to 31 of D5. Hence, Claim 15 lacks novelty.

Claim 16 lacks novelty over D5

78. Page 3, line 31 to page 4, line 3 of D5 indicates that the invention (which includes anti-TACI antibodies for therapeutic purposes) can decrease antibody production. Therefore, Claim 16 lacks novelty.

Claim 17 lacks novelty over D5

79. The treatment of autoimmune disease with anti-TACI antibodies which antagonise TACI activity is disclosed on page 58, line 9 of D5. Thus, Claim 17 lacks novelty.

Claim 18 lacks novelty over D5

80. The treatment of systemic lupus erythematosus, myasthenia gravis and rheumatoid arthritis with anti-TACI antibodies which antagonise TACI activity is disclosed on page 58, lines 10 to 18 of D5. Thus, Claim 18 lacks novelty.

Claim 21 lacks novelty over D5

81. The treatment of myeloma and lymphoma using anti-TACI antibodies which antagonise TACI activity is disclosed on page 58, lines 20 to 22 of D5. Thus, Claim 21 lacks novelty.

Claim 23 lacks novelty over D5

82. The treatment of undesirable immune responses using anti-TACI antibodies which antagonise TACI activity is disclosed on page 58, line 8 of D5. This is "moderating immune response"; thus, Claim 23 lacks novelty.

Claims 27 and 28 lack novelty over D5

83. Page 58, line 10 of D5 describes the treatment of inflammation with anti-TACI antibodies which antagonise TACI activity. In particular, rheumatoid arthritis is associated with joint pain and swelling. Thus, Claims 27 and 28 lack novelty.

Claims 36 to 38 lack novelty over D5

84. Page 58, lines 24 to 28 of D5 describe therapeutic compositions of anti-TACI antibodies. Page 49 line 21 to page 52, line 16 makes it clear that such antibodies include polyclonal antibodies, murine monoclonal antibodies, human antibodies and fragments thereof

including Fab, F(ab')₂ and the like. Thus, Claims 36 to 38 lack novelty.

Claims 36 and 37 lacks novelty over D6

85. D6 (Gras *et al* (1995) *Int. Immunol.* 7, 1093-1106) describes affinity purified anti-BCMA antibodies which were dialysed against phosphate-buffered saline and stored in 50% glycerol (see page 1094, column 2).
86. This is a disclosure of Claims 36 and 37 since this composition of polyclonal antibodies would be pharmaceutically acceptable and so is a pharmaceutical composition.

LACK OF INVENTIVE STEP

Claims 1 and 3 make no technical contribution to the art

87. We refer the OD to T241/95. T241/95 relates to a patent application where the alleged invention was based on the discovery that the (R)-isomer of fluoxetine shows a high specificity for the serotonin 5-HT_{1C} receptor. A claim was made to the use of this compound "*for the preparation of a medicament for treating a mammal suffering from or susceptible to a condition which can be improved or prevented by selective occupation of the 5-HT_{1C} receptor*".
88. The Board of Appeal disapproved of this claim under Article 84 EPC. However, the Reasons for the Decision make it clear that this claim format (ie where a functional feature is used to attempt to define a condition to be treated) also leads to a lack of inventive step and, as discussed later, a lack of sufficiency of disclosure.
89. Section 3.1.2 of the Reasons of Decision notes that:

"The Board wishes to stress that the "selective occupation" of a receptor, although being undisputably a pharmacological effect, cannot in itself be considered a therapeutic application. The discovery on which the invention is based, even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a defined, real treatment of any pathological condition in order to make

a technical contribution to the art and be considered an invention eligible for patent protection” (original emphasis).

90. Claims 1 and 3 of the Patent refer to “inhibiting ztnf4 activity in a mammal” and “inhibiting TACI or BCMA receptor-ztnf4 engagement”. Although the pharmacological effect of the various compounds listed in the claims may be to inhibit ztnf4 activity or to inhibit TACI or BCMA receptor-ztnf4 engagement, these cannot themselves be considered a therapeutic application and do not stipulate a practical application in the form of a defined, real treatment of any pathological condition. Thus, following the logic of T241/95, there is no technical contribution to the art and, we submit, no inventive step. Additionally or alternatively Claims 1 and 3 cannot be considered to be an invention eligible for patent protection (contrary to Article 52(1) EPC) since no defined, real treatment is stipulated in Claims 1 and 3. To put it another way, there is no invention in identifying the mode of action of known or obvious therapeutic agents.

Background to the invention

91. At the priority date of the Patent, it was known that (1) BCMA and TACI were members of the tumor necrosis factor (TNF) receptor family see, for example, Figure 6 of Madry *et al* (1998) *Int. Immunol.* **10**, 1693-1702 (D7); (2) BCMA plays a role in the development and regulation of the immune system, and that it is preferentially expressed in B lymphocytes (D7, last paragraph of Discussion and first sentence of Discussion); (3) TACI is found on B lymphocytes and that it can be targeted to specifically regulate B cell responses without affecting mature T cell activity and that such targeting using anti-TACI antibodies is therapeutically useful (D5; for example page 3, lines 31 to 33; see also von Bülow & Bram (1997) *Science* **278**, 138-141 (D8) which describes the synthesis of specific anti-TACI antibodies in Note 10); and (4) an “orphan” member of the TNF ligand family was known called TL5 (EP 0 869 180 A1; D9) or neutrokin α (WO 98/18921; D10). These are the same as ztnf4 in the Patent (see Table 1 (D1)).
92. In addition, the identification of the cognate ligand for BCMA was clearly desired (last sentence of Discussion of D7), as was the cognate ligand for TACI (see discussion of ligands to the TACI protein on page 52 *et seq* of D5).

93. Furthermore, Mukhopadhyay *et al* (1999) *J. Biol. Chem.* **274**, 15978-15981 (D11; prior art for subject matter not entitled to priority) discloses that ztnf4 (called THANK in D11; see Patent at page 2, line 20) does not bind the TNF receptor (see page 15981, column 1).
94. Also, the targeting of B-cells with antibodies to B-cell specific surface proteins was well known for the treatment of lymphoma (see, US Patent No 5,595,721 (D12) which describes anti-CD20 antibodies).

The closest prior art and problem to be solved

95. D5 can be considered to be the closest prior art since it relates to the use of anti-TACI antibodies which antagonise TACI activity for treating various medical conditions where selective modulation of B cell activity, compared to T cell activity, is desirable.
96. In relation to the embodiments of the claimed invention directed at anti-TACI antibodies (ie antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID No 6), the problem to be solved may be considered to be their use in further medical conditions. These further medical conditions are all ones where selective modulation of B cell activity, compared to T cell antibody, is obviously desirable.
97. In relation to the embodiments of the claimed invention directed at anti-BCMA antibodies (ie antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID No 8), the problem to be solved may be considered to be the provision of an alternative target for antibodies which target is expressed preferentially on B cells and which is known to be involved in immune modulation. D7 strongly suggests that BCMA is a suitable alternative target for antibodies since it is a member of the TNF receptor superfamily, like TACI, is preferentially expressed in B lymphocytes, and is indicated as playing a role in the development and regulation of the immune system.
98. No doubt the Patentee will argue that neither D5 nor D7 disclose that ztnf4 is a ligand for TACI and BCMA and so the claimed invention is not suggested. However, as discussed above, the reference to "inhibiting ztnf4" and "inhibiting TACI or BCMA receptor-ztnf4 engagement" make no technical contribution to the art of treating medical conditions in which case Claims 3 to 28 should be considered as a series of classical second medical use claims directed

at specific diseases, all of which are obvious to attempt to treat with an antibody directed at a receptor expressed preferentially in B-lymphocytes. In any event, the identification of the known "orphan" TNF-like molecule ztnf4 (called TL5 in D9 and neutrokin α in D10 and THANK in D11) as a ligand for BCMA and TACI is not inventive (and indeed was done by the inventors of D2 at substantially the same time as the inventors of the Patent).

99. D12 may also be considered the closest prior art since it describes treating B-cell proliferative diseases with an antibody which targets a B-cell specific surface protein (CD20). In that case, the problem may be considered to be the provision of antibodies to alternative B cell specific proteins for the same purpose.

Claim 1

100. We have already noted that Claim 1 lacks novelty over D5 in relation to anti-TACI antibodies. To the extent that there is any difference between the disclosure of D5 and Claim 1 there is nothing inventive in relation to identifying ztnf4 as a ligand of TACI (or BCMA) since ztnf4 was an obvious candidate "orphan" ligand (see D9 and D10).
101. Claim 1 lacks an inventive step over a combination of D5 and D7 in relation to anti-BCMA antibodies because the skilled person would try to use antibodies directed at BCMA in the same way that they are used against TACI in D5 with a reasonable expectation of success, since BCMA is an alternative target preferentially expressed on B lymphocytes and involved in immune modulation.
102. Both TACI and BCMA are known B-cell specific surface proteins (see D7, D5 and D8) and therefore obvious targets for antibody-based therapies as described in D12. The antibodies described in D12 may be either unlabelled or labelled with a radioisotope (see Abstract). Compare this to the Patent at paragraphs [0089] and [0090]. Since all that is required for antibodies to be useful in this type of therapy is that they bind to B-cell specific surface protein, and since ztnf4 binds to the surface exposed portions of TACI and BCMA, it is inevitable that at least some antibodies would be made using this obvious approach which would inhibit ztnf4 activity (ie inhibit TACI or BCMA receptor-ztnf4 engagement). Thus, Claim 1 lacks an inventive step over a combination of D12 and D7 or D12 and D5 or D8.

Claim 2

103. There is nothing inventive in relation to treating primates, such as humans, which is the thrust of D5 and D12 and an obvious thing to try in any event.

Claim 3

104. We have already noted that Claim 3 lacks novelty over D5 in relation to anti-TACI antibodies. To the extent that there is any difference between the disclosure of D5 and Claim 3, there is nothing inventive in relation to identifying *ztnf4* as a ligand of TACI or BCMA as discussed above and inhibiting TACI or BCMA receptor-*ztnf4* engagement (which anti-receptor antibodies would do).
105. Claim 3 lacks an inventive step over a combination of D5 and D7 in relation to anti-BCMA antibodies for the same reasons as Claim 1 since the skilled person is motivated to use anti-BCMA antibodies.
106. Claim 3 also lacks an inventive step over the combination of D12 and D5 (or D8) or D12 and D7.

Claims 13 to 28

107. We have already shown that Claims 13, 15, 16, 17, 18, 21, 23, 27 and 28 lack novelty over D5.
108. Any diseases or conditions mentioned in the claims which are not disclosed in D5 are nevertheless obvious since they are diseases or conditions known to be associated with B lymphocytes and immune modulation. TACI and BCMA are both known to be specific markers of B cells (ie the proteins are expressed on the surface of B cells only) and so targeting TACI or BCMA with a therapeutic antibody including one which prevents ligand binding is an obviously desirable approach.
109. Similarly, the combination of D5 and D7 makes all of these claims obvious since as discussed in relation to Claims 1 and 3, the use of anti-BCMA antibodies in place of anti-TACI antibodies is obvious, and all of the diseases listed are ones which are associated with B-lymphocytes and immune modulation.

110. In relation to inhibiting effector T cells, effector T cells are activated by certain types of B cells, so that inhibition of B cells leads to inhibition of effector T cells in any event.
111. In addition, D12 specifically relates to the treatment of lymphomas with anti-B cell specific antibodies.

Claims 36 to 38

112. Claims 36 to 38 lack novelty over D5 in relation to anti-TACI antibodies. Since the use of anti-BCMA antibodies and fragments thereof for treating B-lymphocyte related conditions is obvious as discussed above, pharmaceutical compositions of anti-BCMA antibodies and fragments thereof are obvious.
113. In addition, the combination of D6 which discloses anti-BCMA antibody compositions and D5 leads the skilled person to make the compositions of Claims 36 to 38 (if such compositions are not disclosed in D6 in any event).

Antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID No 10

114. We note that Claims 1, 3 and 36, and claims dependent thereon refer to "an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID No 10".
115. SEQ ID No 10 is the polypeptide stipulated as

Xaa	Xaa	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Asp	Xaa	Leu	Leu	Xaa
1			5				10						15		
Xaa	Cys	Xaa	Xaa	Cys	Xaa	Xaa	Xaa	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			20				25						30		
Xaa	Cys	Xaa	Xaa	Xaa	Cys	Xaa	Xaa								
			35				40								

where Xaa is independently any amino acid residue except cysteine, or absent (see page 47, lines 3 to 13 of the Patent). Thus, for example, the polypeptide Cys Asp Leu Leu Cys Cys Cys Cys is included (ie when Xaa is absent) and even for a polypeptide of forty residues there are 19²³ possible combinations if only natural amino acids are considered.

116. Since there is no guidance which of these polypeptides antibodies are to be made to, and there is certainly no evidence that antibodies are

useful in inhibiting ztnf4 activity or receptor-ztnf4 engagement, antibodies to this polypeptide solves no technical problem so there is no inventive step.

117. To the extent that the sequence may encompass TACI or BCMA, the claims lack novelty and inventive step for the reasons given above.

LACK OF SUFFICIENCY OF DISCLOSURE

The Patent does not teach how to inhibit TACI or BCMA receptor-ztnf4 engagement without also inhibiting TACI or BCMA ligand binding generally

118. Claim 3 of the Patent is directed at the manufacture of a medicament for inhibiting TACI or BCMA receptor-ztnf4 engagement. As noted under the section on unallowable addition of subject matter, the term "receptor-ligand engagement" has been replaced with "receptor-ztnf4 engagement" which indicates that a more precise inhibition is contemplated (ie receptor-ztnf4 engagement) rather than inhibition of receptor-ligand engagement generally.
119. Since other ligands bind to the TACI or BCMA receptor at the same site which overlaps with the binding site for ztnf4 (see discussion of D4 at paragraph 41 above) any anti-receptor antibodies which inhibit ztnf4 engagement with the receptor will also inhibit ligand-receptor engagement *generally* and there is no disclosure in the Patent of how to *selectively* inhibit receptor-ztnf4 engagement.
120. In any event, there is no disclosure whatsoever in the Patent of anti-BCMA antibodies which inhibit ztnf4 activity or which inhibit BCMA-ztnf4 engagement and so all of the claims which encompass this feature lack sufficiency.

The Patent does not teach how to identify medical conditions which require inhibition of ztnf4 activity or TACI or BCMA receptor-ztnf4 engagement

121. We refer again to T241/95 and, in particular, the penultimate paragraph of Section 3 of the Reasons for the Decision which states:

"Under these circumstances [ie where there are not cited or known tests to determine whether a medical condition

satisfies the functional definition], *the Board is of the opinion that at the filing date of the application no means involving testable criteria existed to assist the skilled person in assessing whether or not a "condition" improved or prevented by (R)-fluoxetine was comprised in the functional definition of the claimed subject matter.*

For these reasons, the Board holds that claim 1 does not meet the requirements of Article 84 EPC."

122. An equivalent situation occurs in respect of Claims 1 and 3 of the Patent since there are no means involving testable criteria which assist the skilled person in assessing whether a "condition" is one which would benefit from the inhibition of ztnf4 activity or TACI or BCMA receptor-ztnf4 engagement.
123. We, of course, appreciate that Article 84 EPC as such is not a ground of opposition. However, it is clear that an equivalent objection applies under Article 83 EPC since, objectively, if the skilled person is not able to determine which medical conditions are ones where inhibition of ztnf4 activity or TACI or BCMA receptor-ztnf4 engagement is beneficial, he cannot carry out the invention across the scope of the claim.

The patent does not teach how to make and use medicaments containing anti-BCMA antibodies or anti-TACI antibodies

133. There is no technical teaching in the Patent which indicates that anti-BCMA antibodies have any pharmacological effect or would be useful in the treatments claimed. No anti-BCMA antibodies have been made or tested and any alleged therapeutic effect or utility is mere speculation on the part of the Patentee. The same is true for anti-TACI antibodies.
134. It is well established (eg from T409/91 and T435/91) that the protection conferred by a patent should correspond to the technical contribution to the art made by the disclosure of the invention described therein, which excludes the patent monopoly being extended to subject matter which, after reading the patent specification, would still not be at the disposal of the skilled person.
135. Thus, at least in relation to anti-BCMA antibodies, the protection conferred by the Patent does not correspond to the technical contribution to the art since no technical contribution has been made.

All claims which refer to anti-BCMA antibodies (ie Claims 1 to 3, 13 to 28, and 36 to 38 which refer to an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID No 8) do not, therefore, satisfy Article 83 EPC (Article 100(b) EPC).

There is no disclosure of any antibodies or antibody fragments which specifically bind the "polypeptide" of SEQ ID No 10

136. As noted above, SEQ ID No 10 represents a myriad of possible polypeptides from as short as 9 amino acid residues to 40 residues. There is no disclosure of any antibodies directed at any of these polypeptides and certainly no teaching of which ones may be useful in inhibiting ztnf4 activity or inhibiting receptor-ztnf4 engagement or how to identify such antibodies. Thus, there is an insufficient disclosure of this embodiment of the invention.

Apart from in the sequence listing and claims, there is no disclosure of the polypeptide of SEQ ID No 20

137. There is no disclosure of the polypeptide of SEQ ID No 20 in the description of the Patent and therefore no guidance on how to make and use antibodies thereto. The Patent is insufficient for this reason also.

SUMMARY

138. The Patent should be revoked under Articles 100(a), (b) and (c) EPC.

DOCUMENTS REFERRED TO

- D1 Table
D2 WO 01/12812 (EP 1 210 425 A)
D2a US Patent Application No 60/149,378
D3 WO 01/24811 (EP 1 223 964 A)
D3a US Patent Application No 60/157,933
D4 Patel (2004) *J. Biol. Chem.* **279**, 16727-16735

- D5 WO 98/39361
- D6 Gras *et al* (1995) *Int. Immunol.* **7**, 1093-1106
- D7 Madry *et al* (1998) *Int. Immunol.* **10**, 1693-1702
- D8 von Bülow & Bram (1997) *Science* **278**, 138-141
- D9 EP 0 869 180
- D10 WO 98/18921
- D11 Mukhopadhyay *et al* (1999) *J. Biol. Chem.* **274**, 15978-15981
- D12 US Patent No 5,595,721
- D13 Alignment of human and mouse TACI

John S Miles